Nuclear Magnetic Resonance Principles

Introduction

Nuclear magnetic resonance (NMR) is a physical [resonance](#) phenomenon involving the observation of nuclear spin transitions induced by the absorption of radio frequency quanta by atomic nuclei interacting also with an external (either static or gradient) magnetic field.

NMR is thus commonly referred to as ``a family of scientific methods and techniques that exploit the nuclear magnetic resonance resonance phenomenon to study molecules in solutions, gases, crystals, liquid crystals, nanomaterials, superconductors, and non-crystalline materials''.

NMR spectroscopy- the automated recording and analysis of NMR spectra- is the most important (as well as routine) group of techniques in this family, based on the observation of the important property of chemical shift caused by molecular (electron) orbitals. All nuclei that contain odd numbers of protons and/or neutrons have a non-zero intrinsic magnetic moment and angular momentum, in other words a spin >0 which takes on either $(k+1)$ or $(k+1/2)$ values, with $k=0,1,2,...,n$. The most commonly measured nuclei are $_1H$ (the most NMR-sensitive isotope after the radioactive $_3H$ isotope, and also after the stable $_{13}$ C nucleus, although nuclei from isotopes of many other elements (for example: $_2$ H, $_7$ Li, $_{10}$ B, $_{11}$ B, $_{14}$ N, $_{15}$ N, $_{17}$ O, $_{19}$ F, $_{23}$ Na, $_{29}$ Si, $_{31}$ P, $_{35}$ Cl, $_{37}$ Cl, $_{43}$ Ca, $_{81}$ Br, $_{113}$ Cd, $_{195}$ Pt) are readily measured by high-field NMR spectroscopy as well. NMR resonant frequencies for a particular substance are directly proportional to the strength of the applied magnetic field, in accordance with the equation for the Larmor precession frequency. The scientific literature as of February 2009 includes NMR spectra at magnetic fields in a wide range: from about 5 nT up to 24 T. Very high magnetic fields are often preferred since 1D-NMR detection sensitivity increases proportionally with the magnetic field strength (the ``Golden Rule of NMR''). Other methods to increase either the NMR signal strentgth or the detection sensitivity include hyperpolarization and two-dimensional (2D) FT NMR techniques. The NMR phenomenon involves two principal sequential steps: (1) the alignment or polarization of the magnetic nuclear spins being studied in an applied, constant magnetic field $\mathbf{H}_0$, and (2) the perturbation

of this alignment of the nuclear spins (in the constant external magnetic field) by employing a second, alternating magnetic field (rf) $\mathbf{H_{1rf}}$, with the two fields being usually orthogonal for maximum detected NMR signal intensity. A powerful rf transmitter produces the rf field $\mathbf{H_{1rf}}$ and is thus the forcing oscillator which resonates with the coupled (forced, or perturbed) system of nuclear spins whose total (macroscopic) magnetization $\mathbf{M}=M_{\rightarrow}$ oscillates at the intrinsic (Larmor) frequency ν_0 in the form of a Larmor precession of $M_{\rightarrow}$ around the applied magnetic field $\mathbf{H_0}$ (selected as the z-axis). When the `carrier frequency' ν_2 of the rf transmitter matches the Larmor frequency ν_0, the latter transmits energy at resonance to the (coupled) nuclear spin system that absorbs the rf energy and $M_{\rightarrow}$ is tilted to the y direction in the (x,y) plane (normal to z) for the duration of the rf transmitter strong rf perturbation. This resulting response by the total magnetization, $M=M_{\rightarrow}$, of the (coupled) nuclear spins to the strongly perturbing magnetic field $\mathbf{H_{1rf}}$ is the resonance phenomenon that is exploited both in NMR spectroscopy and magnetic resonance imaging, which both use intense applied magnetic fields $\mathbf{H_0}$, in order to achieve high spectral resolution, the details of which are described by the chemical shift, the Zeeman effect, and Knight shifts (in metals). Nuclear magnetic resonance was first described and measured in molecular beams by Isidor Rabi in 1938.

Nuclear Magnetic Resonance Theory

Nuclear spins and magnets

All nucleons, that is the neutrons and protons composing an atomic nucleus, have the intrinsic quantum mechanical property of spin. The overall spin of the nucleus is determined by the spin quantum number, I. If the number of both the protons and neutrons in a given isotope are even then $I=0$, i.e. there is no overall spin; just as electrons pair up in atomic orbitals, so do even numbers of protons and neutrons (which are also spin 1/2 particles and hence fermions) pair up giving zero overall spin. In other cases, however, the overall spin is non-zero. For example 17 O has a spin $I=5/2$.

A non-zero spin, I, is associated with a non-zero magnetic moment, μ, via

$$\mu=\gamma I,$$

where the proportionality constant, γ, is the gyromagnetic ratio.

It is this magnetic moment that allows the observation of NMR absorption spectra caused by transitions between nuclear spin levels. Most radioactive nuclei (with some rare exceptions, such as tritium) that have both even numbers of protons and even numbers of neutrons, also have zero nuclear magnetic moments-and also have zero magnetic dipole and quadrupole moments; therefore, such radioactive isotopes do not exhibit any NMR absorption spectra. Thus, $_{12}$C,$_{32}$P and $_{36}$Cl are examples of radioactive nuclear isotopes that have no NMR absorption, whereas $_{13}$C, $_{31}$P, $_{35}$Cl and$_{37}$Cl are stable nuclear isotopes that do exhibit NMR absorption spectra.

Electron spin resonance is a related technique which detects transitions between electron spin levels instead of nuclear ones. The basic principles are similar; however, the instrumentation, data analysis and detailed theory are significantly different. Moreover, there is a much smaller number of molecules and materials with unpaired electron spins that exhibit ESR (or EPR) absorption than those that have NMR absorption spectra. Significantly also, is the much greater sensitivity of ESR in comparison with NMR. Furthermore, ferromagnetic materials and thin films may exhibit highly resolved ferromagnetic resonance (FMR) spectra, or spin wave excitations (SWR) beyond the single-quantum transitions common to most routine NMR and EPR studies.

Permitted values of the spin angular momentum

The angular momentum associated with nuclear spin is quantized. This means both that the magnitude of angular momentum $\mathbf{I}$ is quantized (that is, I can only take on a restricted range of values), and also that the `orientation' of the associated angular momentum is quantized. The associated quantum number is known as the magnetic quantum number, m , and can take values from +I to -I in integral steps. Hence for any given nucleus, there is a total of $2I+1$ angular momentum states.

The z - component of the angular momentum vector, $\mathbf{I}$ is therefore: $I_z = mh/(2\pi)$, where h is Planck's constant.

The z -component of the magnetic moment is simply:
$$\mu_z = \gamma I_z = hm\gamma/(2\pi).$$

Nuclear spin interactions with a magnetic field

Consider nuclei which have a spin of one-half, like $_1$H, $_{13}$C or $_{19}$F. The nucleus has two possible spin states: $m=1/2$ or $m=-1/2$ (also referred to as up and down or α and β, respectively). The energies of these states are degenerate (that is, they are the same). Hence the populations of the two states (that is, the numbers of atoms in the two states) will be approximately equal at thermal equilibrium.

If a nucleus is placed in a magnetic field, however, the interaction between the nuclear magnetic moment and the external magnetic field mean the two states no longer have the same energy. The energy of a magnetic moment μ when in a magnetic field $\mathbf{B}_0$ (the zero subscript is used to distinguish this magnetic field from any other applied field) is given by the negative scalar product of the vectors:

$$E=(-1)\vec{\mu} \cdot \vec{B_0},$$

or

$$E=(-1)\mu_z B_0,$$

where the magnetic field has the orientation along the z axis.

Hence: $E=(-1)hm/(2\pi)\gamma B_0$.

As a result the different nuclear spin states have different energies in a non-zero magnetic field. One can simply describe the two spin states of a spin 1/2 as `being aligned either with or against the applied magnetic field'.

If γ is positive (true for most isotopes) then $m=1/2$ is the lower energy state.

The energy difference between the two states is:

and this difference results in a small population bias toward the lower energy state.

Resonance

Resonant absorption will occur when electromagnetic radiation of the correct frequency to match this energy difference is applied. The energy of a photon is $E=h\nu$, where ν is its frequency. Hence absorption will occur when

. These frequencies typically correspond to the radio frequency range of the electromagnetic spectrum for magnetic fields

up to about 20T. It is this (magnetic) resonant absorption that is detected in NMR.

Nuclear shielding by electron orbitals

It might appear from the above that all nuclei of the same nuclide (and hence the same γ) would resonate at the same frequency. This is not the case. The most important perturbation of the NMR frequency for applications of NMR is the `shielding' effect of the surrounding electrons. In general, this electronic shielding reduces the magnetic field at the nucleus (which is what determines the NMR frequency). As a result the energy gap is reduced, and the frequency required to achieve resonance is also reduced. This shift in the NMR frequency due to the electron (molecular) orbital coupling to the external magnetic field is called chemical shift, and it explains why NMR is able to probe the chemical structure of molecules which depends on the electron density distribution in the corresponding molecular orbitals. If a nucleus in a specific chemical group is shielded to a higher degree by a higher electron density of its surrounding moelcular orbital, then its NMR frequency will be shifted upfield (that is, a lower chemical shift), whereas if it is less shielded by such surrounding electron density, then its NMR frequency will be shifted downfield (that is, a higher chemical shift will be measured).

Unless the local symmetry of such molecular orbitals is very high (that is, in the `isotropic shift' case), the shielding effect will depend on the orientation of the molecule with respect to the external field, $\mathbf{H}_0$. In solid-state NMR spectroscopy, magic angle spinning is required to average out this orientation dependence in order to obtain values close to the average chemical shifts. This is obviously unnecessary in conventional NMR of molecules in solution since rapid molecular tumbling averages out the chemical shift anisotropy (CSA) to the `average chemical shift' (ACS).

NMR spectroscopy methods

NMR spectroscopy is one of the principal techniques used to obtain physical, chemical, electronic and structural information about molecules due to the chemical shift Zeeman effect, and/or Knight shift effect on the resonant frequencies of the nuclei present in the sample. It is a powerful set of techniques and methods that can provide detailed information on the topology, dynamics,three-dimensional structure of molecules in solution and the solid state, as well as on chemical kinetics. Thus, structural and dynamic information is obtainable (with or without magic-angle spinning

(MAS, or M.A.S.S)) from NMR studies of quadrupolar nuclei (that is, those nuclei with spin I > 1/2, such as 1, 3/2, 5/2, and so on) even in the presence of dipolar broadening which is always much smaller than the quadrupolar interaction strength.

Additional structural and chemical information may be obtained by performing double-quantum NMR experiments for quadrupolar nuclei such as $_2$ H.

Also, nuclear magnetic resonance is one of the techniques that has been used to build elementary quantum computers [reference].

Fourier Transform (FT) Spectroscopy

Applications of NMR usually involve full-range spectra, that is, the intensity of the NMR signal as a function of frequency needs to cover the entire range of chemical shift values of the molecules being investigated. Early attempts to acquire the NMR spectrum more efficiently than simple CW methods involved irradiating simultaneously with more than one frequency. It was soon realised, however, that a simpler solution was to use short pulses of radio-frequency (centred at the middle of the NMR spectrum). In simple terms, a short `square' pulse of a given ``carrier frequency signal'' consists in fact in a whole range of frequencies centered about the carrier frequency, with the range of excitation or bandwidth being inversely proportional to the pulse duration (for example, the Fourier transform of an approximate square wave contains contributions from all the frequencies in the neighborhood of the principal frequency). The restricted range of the NMR frequencies made it relatively easy to use short (millisecond to microsecond) radiofrequency (RF) pulses to excite the entire NMR spectrum.

Applying such an rf pulse to a set of nuclear spins simultaneously excites all the single-quantum NMR transitions. In terms of the net magnetisation vector, this corresponds to tilting the magnetisation vector away from its equilibrium position (aligned along the external magnetic field). The out-of-equilibrium magnetization vector precesses about the external magnetic field vector at the NMR frequency of the spins. This oscillating magnetization vector induces a current in a nearby pickup coil, creating an electrical signal oscillating at the NMR frequency. This signal is known as the free induction decay (FID) and contains the vector-sum of the NMR responses from all the excited spins. In order to obtain the frequency-domain NMR spectrum (NMR absorption intensity vs. NMR frequency) this

time-domain signal (intensity vs. time) must be Fourier transformed. Fortunately the development of FT-NMR coincided with the development of digital computers and Fast Fourier Transform algorithms.

Richard R. Ernst was one of the pioneers of pulse (FT) NMR and won a Nobel Prize in chemistry in 1991 for his work on FT-NMR and his development of multi-dimensional NMR (see below).

Multi-dimensional NMR Spectroscopy

The use of pulses of different shapes, frequencies and durations in specifically-designed patterns or pulse sequences allows the spectroscopist to extract many different types of information about the molecule.

Multi-dimensional nuclear magnetic resonance spectroscopy is a group of FT-NMR techniques (2D-, 3D- ..., FT) in which there are at least two sequential pulses-a preparation and an observation pulse, with the pulse sequence being varied at successive acquisitions of the NMR time-domain signal (FID). Thus, in multi-dimensional nuclear magnetic resonance, one will employ a sequence of pulses and, at least one variable time period. In three dimensions, two time sequences will be varied. In four dimensions, three will be varied, and so on.

There are many such possible multi-D FT-NMR experiments. In one, these time intervals allow-among other things- the magnetization transfer between nuclei and, therefore, the detection of the types of nuclear-nuclear interactions that allowed for the magnetization transfer. Interactions that can be detected are usually classified into two types. There are both ``through-bond'' interactions and ``through-space'' interactions, the latter involving the so called **nuclear Overhauser effect**. Experiments of the nuclear-Overhauser (NOE) variety may be employed to establish distances between atoms for small molecules in solution.

Initially, the fundamental concept of 2D-FT NMR was communicated as a proposed experiment at an NMR conference by the Belgian NMR scientist Jean Jeener, Professor from the Free University of Brussel; this idea was later extensively developed and advanced experimentally by Richard Ernst who won the 1991 Nobel prize in Chemistry for his work in multi-dimensional FT-NMR. Multi-dimensional FT-NMR experiments were further developed into powerful methodologies for studying biomolecules in

solution, in particular for the determination of the structure of biopolymers such as proteins or small nucleic acids.

Kurt Wüthrich shared in 2002 (with John B. Fenn) the Nobel Prize in Chemistry for his work on proteins by 2D -FT nuclear magnetic resonance spectroscopy.

Solid-state NMR spectroscopy

This technique complements biopolymer X-ray and neutron crystallography in that it is frequently applicable to biomolecules in a liquid or liquid crystal phase, whereas crystallography, as the name implies, is performed on molecules in a solid phase. Though nuclear magnetic resonance is used to study solids, extensive atomic-level biomolecular structural detail is especially challenging to obtain in the solid state. There is little signal averaging by thermal motion in the solid state, where most molecules can only undergo restricted vibrations and rotations at room temperature, each in a slightly different electronic environment, therefore exhibiting a different NMR absorption peak. Such a variation in the electronic environment of the resonating nuclei results in a blurring of the observed spectra-which is often only a broad Gaussian band for non-quadrupolar spins in a solid- thus making the interpretation of such ``dipolar and chemical shift anisotropy (CSA)'' broadened spectra either very difficult or impossible. The solution to this problem is presented next.

Magic Angle Spinning

Professor Raymond Andrew at Nottingham University in UK pioneered the development of high-resolution solid-state nuclear magnetic resonance. He was the first to report the introduction of the `magic-angle' spinning (MAS) (or $MASS$) technique that allowed him to achieve spectral resolution in solids sufficient to distinguish between chemical groups with either different chemical shifts or distinct Knight shifts. In MAS, the sample is spun at several kilohertz around an axis that makes the so-called `magic angle' with the static magnetic field $H_0 \rightarrow$, whereby the chemical shift ansiotropy is averaged to its corresponding isotropic chemical shift average value for each chemical group or site if the magic angle sample spinning rate is at least as high as the CSA value expressed in Hz ($s-1$)units. In MAS, the sample is spun at several kilohertz around an axis that makes the so-called

magic angle θ_m (which is 54.74Â°, where $(cos\theta_m)_2=1/3$, (or $3[(cos\theta_m)_2]-1=0$) with respect to the direction of the static magnetic field H0. As a result of such magic angle sample spinning, the chemical shift anisotropy bands are averaged to their corresponding average (isotropic) chemical shift values. The above expression involving $(cos\theta_m)_2$ has its origin in a calculation that predicts the magnetic dipolar interaction effects to cancel out for the specific value of Î¸m called the magic angle. One notes that correct alignment of the sample rotation axis as close as possible to θ_m is essential for cancelling out the dipolar interactions whose strength for angles sufficiently far from θ_m is usually greater than 10 kHz for C-H bonds in solids, for example, and it is thus greater than their CSA values. Subsequently, Alex Pines, M.G. Gibby and John S. Waugh at MIT utilized a concept initially developed by Sven Hartmann and Erwin Hahn to transfer magnetization from protons to less sensitive nuclei (commonly known as `cross-polarization'). then, Schaefer and coworkers demonstrated the powerful use of cross-polarization under MAS conditions (as well as double cross-polarization such as $_1H \longrightarrow _{13}C \longrightarrow _{15}N$) which is routinely used at present to detect low-abundance and low-sensitivity nuclei such as, for example, $_{13}$ C and $_{15}$ N.

Note:

This object is based in part on the author' s contributions on this theme at another GNUL website entry, however with substantial editing and additions. (Relevant literature and color illustrations can also be obtained via the above link.)